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The recognition of nitronate anions by cations derived from bicyclic amidine and guanidine bases has been studied by NMR, X-ray crystallography and semi-empirical molecular orbital theory. It has been clearly established that anions and cations form tightly-organised complexes by formation of pairs of parallel hydrogen bonds. A chiral bicyclic C_2-symmetric guanidine has been synthesized in optically pure form from an α-amino acid starting material. It has been shown to complex carboxylic acids, and to catalyse the conjugate addition of nitroalkanes to electron-deficient alkenes with modest enantioselectivies.

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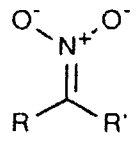
FINAL REPORT

Introduction

The development of enantioselective catalytic synthetic methodology is widely recognised as one of the most important objectives of modern organic chemistry. The establishment of the correct absolute stereochemistry in a target molecule is arguably the most challenging problem in organic synthesis, and methods which are not only effective but also catalytic in nature (and thus applicable on a large scale) are keenly sought. The aim of this project was to investigate and exploit a new phenomenon in molecular recognition which we felt could lead to enantioselective catalysis of reactions of nitroalkanes. Nitroalkanes are valuable in organic synthesis as intermediates for a variety of molecular targets, and are important in their own right as energetic materials. The ability to modify them in a sterocontrolled fashion in bulk-scale chemical processes would have implications for many areas of chemical technology.

The phenomenon underlying the project was the recognition and binding of nitronate anions **1** by bicyclic amidinium and guanidinium ions of general form **2**. Nitronate anions **1** are produced by deprotonation of nitroalkanes, are nucleophilic on the carbon α to nitrogen and may be used in a number of carbon-carbon bond-forming reactions. They bear a negative charge which is substantially located on the two oxygen atoms, giving them a fairly close resemblance to carboxylate ions **3**. Amidinium and guanidinium ions are well known as partners for carboxylates in molecular recognition, the prototypical example being the formation of salt bridges involving arginine residues in proteins. As illustrated in **4**, the components are held together by two parallel hydrogen bonds in addition to the electrostatic attraction. Noting the similarity between nitronates and carboxylates, we argued that the former might also associate with amidinium/guandinium ions, as in complexes **5**. These complexes would presumably be intermediates in nitroalkane reactions catalysed by the amidine/guanidine bases. Given the close, predictable association between cation and anion in **5**, it seemed likely that properly designed chiral analogues might react in an enantioselective fashion with approaching electrophiles. The corresponding amidine/guanidine bases would therefore act as enantioselective catalysts for the reactions.

Preliminary experiments indicated that two achiral bicyclic bases, guanidine **6** and amidine **7**, could indeed deprotonate nitroalkanes to form complexes **5** in non-polar solvents. On this basis, with financial assistance from the USAF and US army, we undertook to (a) characterise the recognition phenomenon as fully as possible by theoretical and experimental means, and (b) design and synthesize a homochiral bicyclic



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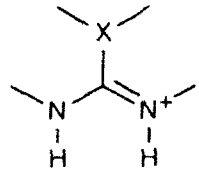
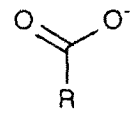


2 X = CR; amidinium
X = N; guanidinium



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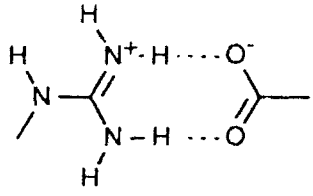

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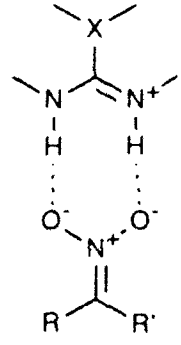

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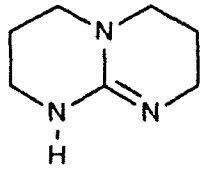
guanidine intended as an enantioselective catalyst for the conjugate addition of nitroalkanes to electron-deficient alkenes (Scheme 1). It was envisaged that, if successful, the project might lead to methods for novel energetic materials such as stereoregular nitro-bearing polymers **8** (Scheme 2).



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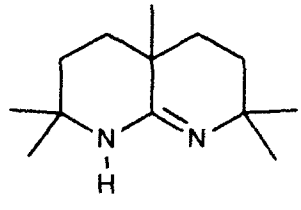

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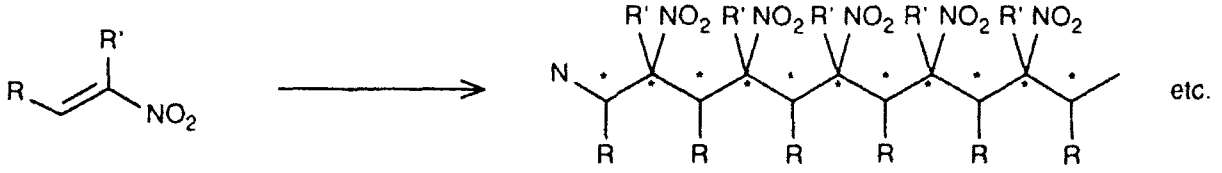
Results and Discussion

(a) *The Recognition Phenomenon; Experimental and Theoretical Characterisation:*

(i) *Studies in non-polar solvents.* Much of this work has been published in a preliminary communication[1] which is included as an Appendix to this report. In brief, comparisons were made between bases **6** and **7**, which are structurally competent to form complexes **5**, and tertiary controls **9** and **10** which can only provide a single H-bond donor site after protonation. Nitroethane **11** was added to these bases in C_6D_6 or

E = electron-withdrawing group

Scheme 1

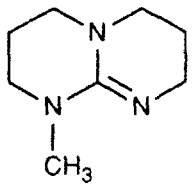


8 N = nucleophilic initiator
* = asymmetric centres with defined stereochemistry

Scheme 2

CD_3CN, and α-deprotonation was detected by the disappearance of $CH_3CH_2NO_2$ and appearance of $CH_3CH{=}NO_2^-$ ^1H NMR signals. Bases **6** and **7** were consistently more effective at generating the $CH_3CH{=}NO_2^-$ signal by a very substantial margin. We argued that as neither **6** nor **7** should be instrinsically more basic than its control, the difference must be due to a special stabilising interaction between **6/7**.H^+ and the nitronate anion. The formation of complexes **12** and **13** was clearly indicated.

An aspect of the work which was not described in the communication was our analysis of the concentration-dependence of proton transfer. We reasoned that if our hypothesis was correct, proton transfer should be giving a single species and should therefore be subject to an "associative" equilibrium constant K_1 (Eqn. 1). On the other hand, if it was occurring to give separate anions and cations then it would not involve a change in the number of species and would be subject to equilibrium constant K_2 (Eqn. 2). In the case of Eqn. 2 the extent of reaction should be independent of concentration, while for Eqn. 1 dilution should favour the left hand side. A study of the proton transfer equilibrium between nitroethane and amidine **7** in C_6D_6 at various concentrations showed that, as expected, the extent of reaction did indeed vary significantly.



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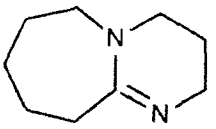

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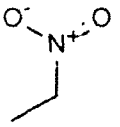

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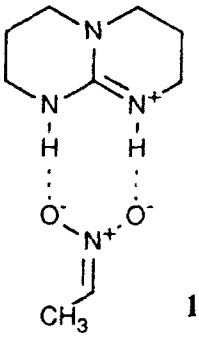

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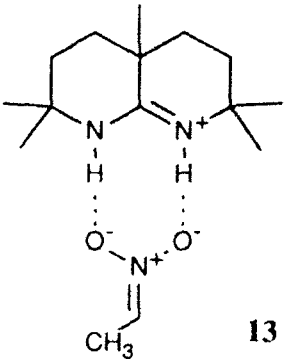

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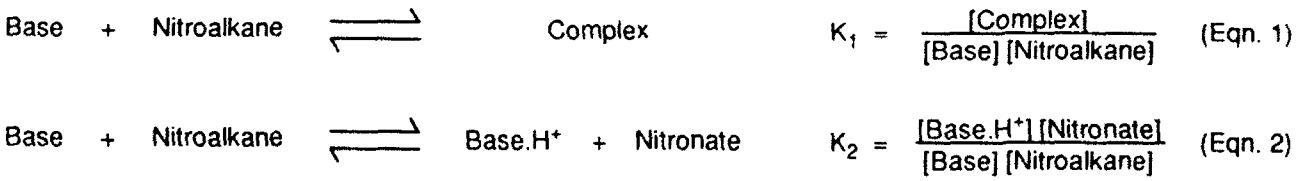
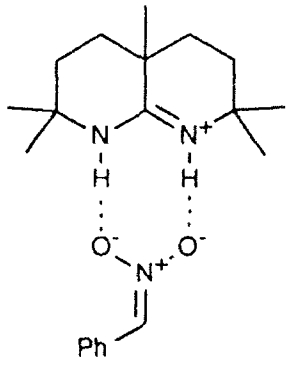
Accordingly K_2 showed a steady movement throughout the range while K_1 was fairly constant, providing further support for our hypothesis.



(ii) *Studies in the solid state*. Again, the details of this work[1] may be found in the Appendix. One of the earliest observations in favour of our hypothesis was that amidine **7** and nitroethane, which are both liquids, instantaneously reacted to give a white solid on mixing. This suggested the possibility of obtaining a crystal structure of one of the complexes, enabling us to make a direct observation of the H-bonding pattern. After trying a number of combinations we were successful in crystallising complex **14**, derived from **7** and phenylnitromethane. The X-ray crystal structure, shown in the Appendix, was in accord with our expectations. As well as revealing the two parallel H-bonds it showed the two components to be roughly coplanar, consistent with the expected preference of H-bonds to be linear.



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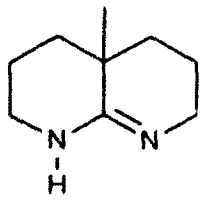
(iii) *Computational studies.* For further characterisation of complexes **5** we turned to semi-empirical molecular orbital theory. We were interested to find how well the theory could reproduce the experimental results (notably the crystal structure), and how far it could be relied upon in future design work. In addition there were questions which could not be answered in other ways, such as the energetic penalty of disorting the H-bonds from a linear arrangement. Surveys were carried out of the complex derived from amidine **15** and nitromethane, using both AM1 and PM3 methodology. Perhaps the most significant result was that, according to both methods, the global minimum was not the "amidinium.nitronate" complex **16** but the "amidine.aci-nitro" combination **17**. According to PM3, which is reported to be more reliable than AM1 for hydrogen bonding systems,[2] **17** is more stable than **16** by *ca.* 10 Kcal mol^{-1}. It is not easy to obtain experimental confirmation of this result because of the difficulty of locating hydrogens by X-ray crystallography. However, the calculated geometry of **17** is quite close to that observed in the crystal structure of **14**, whereas in **16** the planes of cation and anion are at a greater angle with respect to each other. A PM3 minimisation of **14** itself in "amidine.aci-nitro" form resulted in a satisfactory degree of correspondence with the crystal structure, encouraging us to suppose that this method will be useful in future work.



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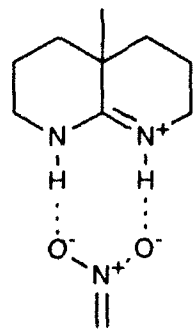

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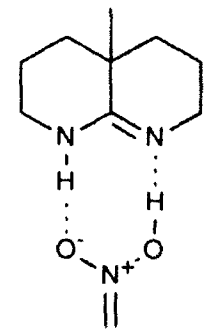

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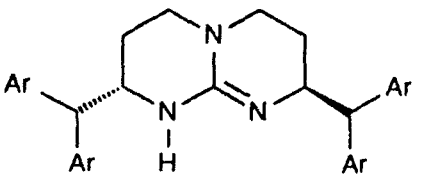
Details of these studies will be combined with an account of the NMR work in a full paper which will be submitted for publication in the near future.

(b) ***An Enantioselective Catalyst for Nitroalkane Reactions:***

(i) *Design considerations.* The most important goal of this project was to design and synthesise an effective enantioselective catalyst for the conjugate addition of nitroalkanes to electron-deficient alkenes. As our starting point we took the bicyclic guanidine framework of **6**. It seemed desirable to maintain a bicyclic structure in which parallel H-bonding capability would be enforced, and model studies on **6** itself had confirmed that it was catalytically active in nitroalkane addition reactions. In order to develop enantioselectivity, we argued that the first step should be to introduce asymmetrically disposed substituents capable of interfering sterically with the area of space around the nucleophilic carbon of the bound nitronate anion (or aci-nitro compound). To ensure that an incoming electrophile could not avoid these groups, it would be preferable to aim for C2-symmetric structures in which both faces of the nitronate would be affected. Our design criteria seemed to be fulfilled by guanidines of general form **18**. A molecular modelling study of the cation **19**, derived from a simple, mono-substituted analogue, confirmed that one of the aromatic rings of the diarylmethyl groups would tend to be extended in a direction roughly parallel to the N-H bond, and that even a phenyl group should be large enough to influence the reactivity of a bound nitronate. On this basis we decided to proceed with the synthesis of **18** (Ar = Ph), assess its properties as a nitronate receptor and catalyst, and use this experience to guide further developments.



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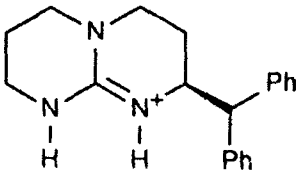

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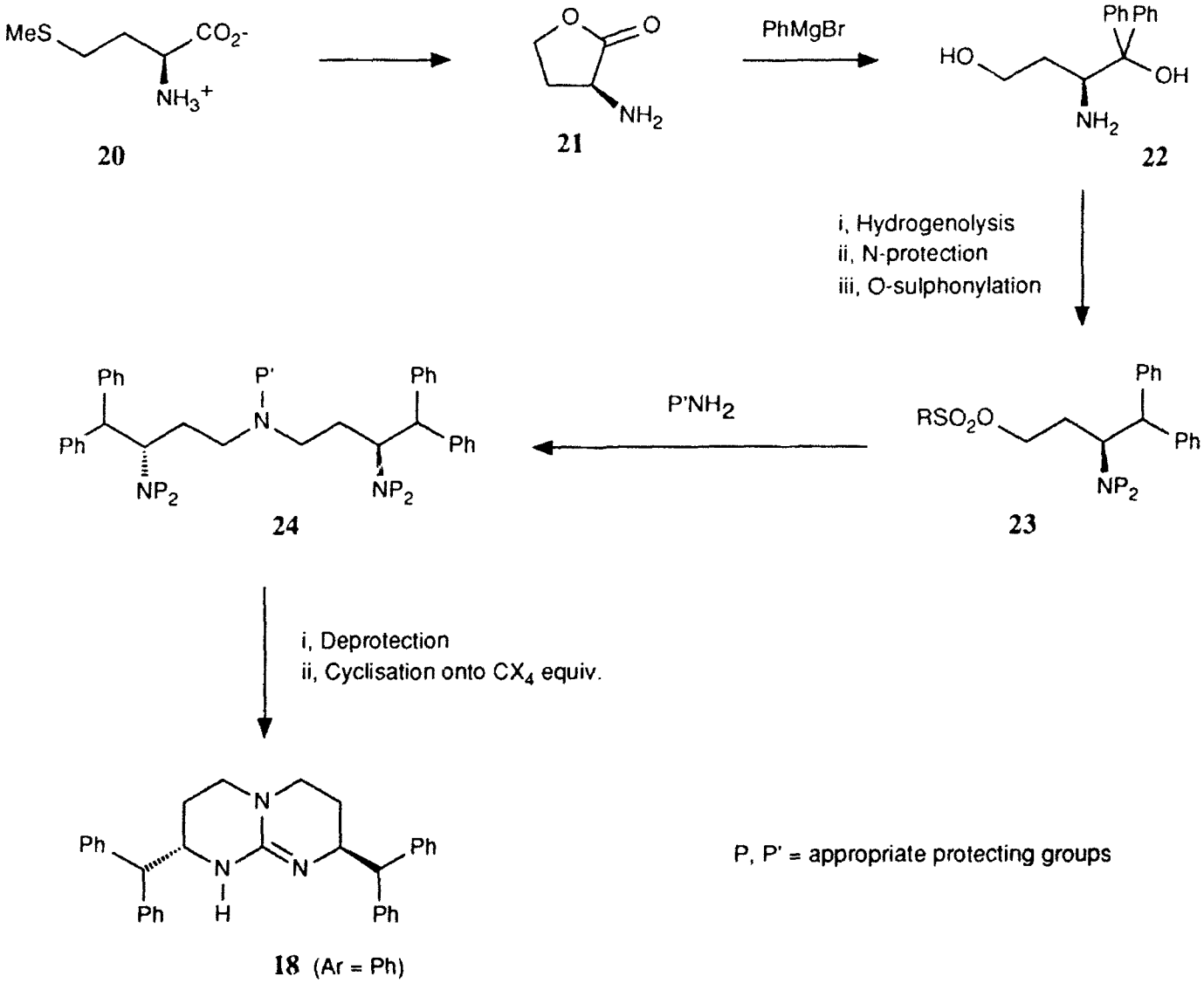
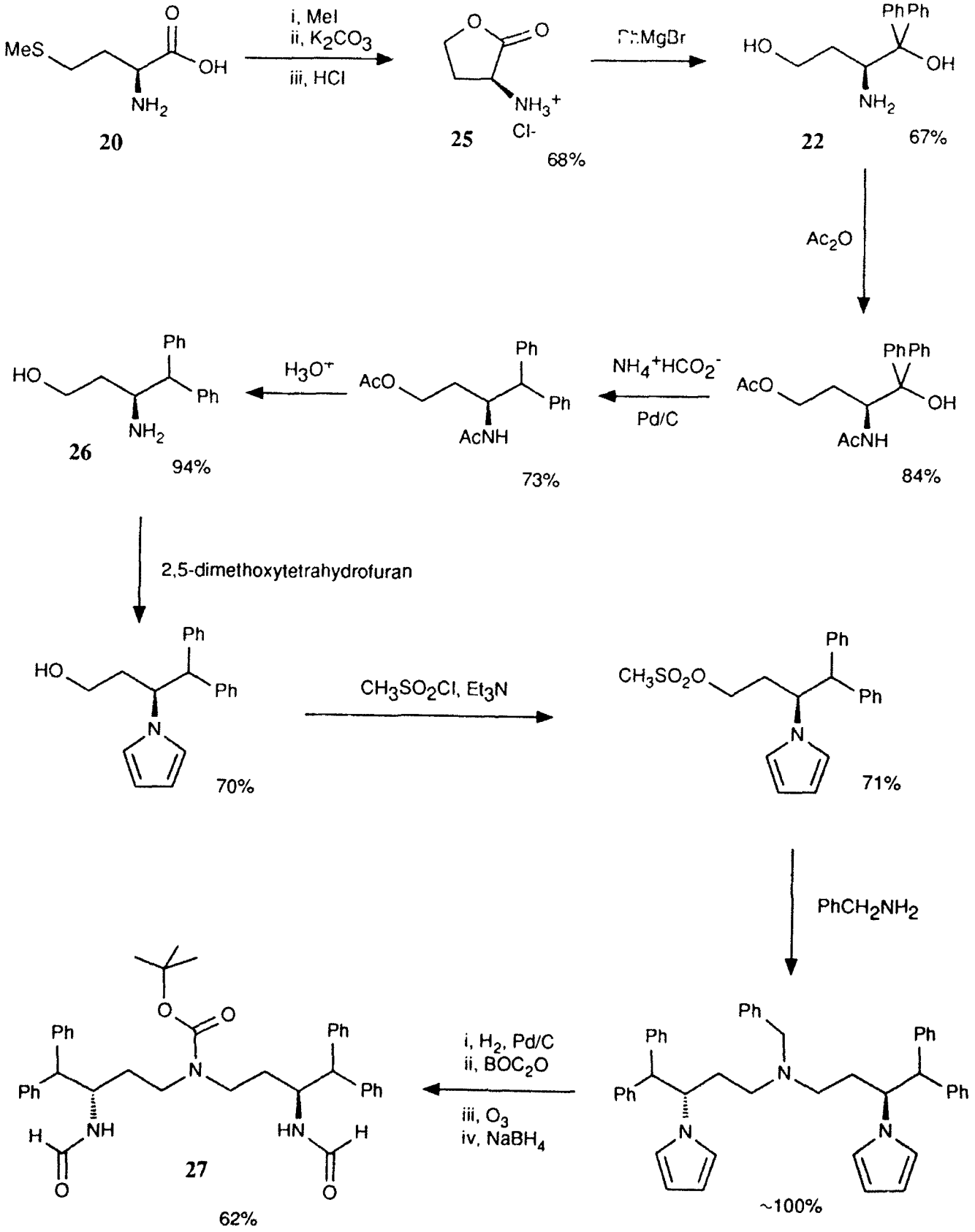
(ii) *Synthesis of* **18** *(Ar = Ph).* An outline of our proposed synthesis is shown in Scheme 3. L-Methionine (**20**) was to be used as an inexpensive chiral starting material. Conversion to L-homoserine lactone (**21**) was a fairly well-established transformation,[3] and there was literature precedent for the bis-addition of organometallic reagents to α-amino acid derivatives (as in formation of **22**).[4] Hydrogenolysis of the doubly

benzylic centre in **22** did not seem unrealistic, and none of the subsequent steps appeared unduly difficult.

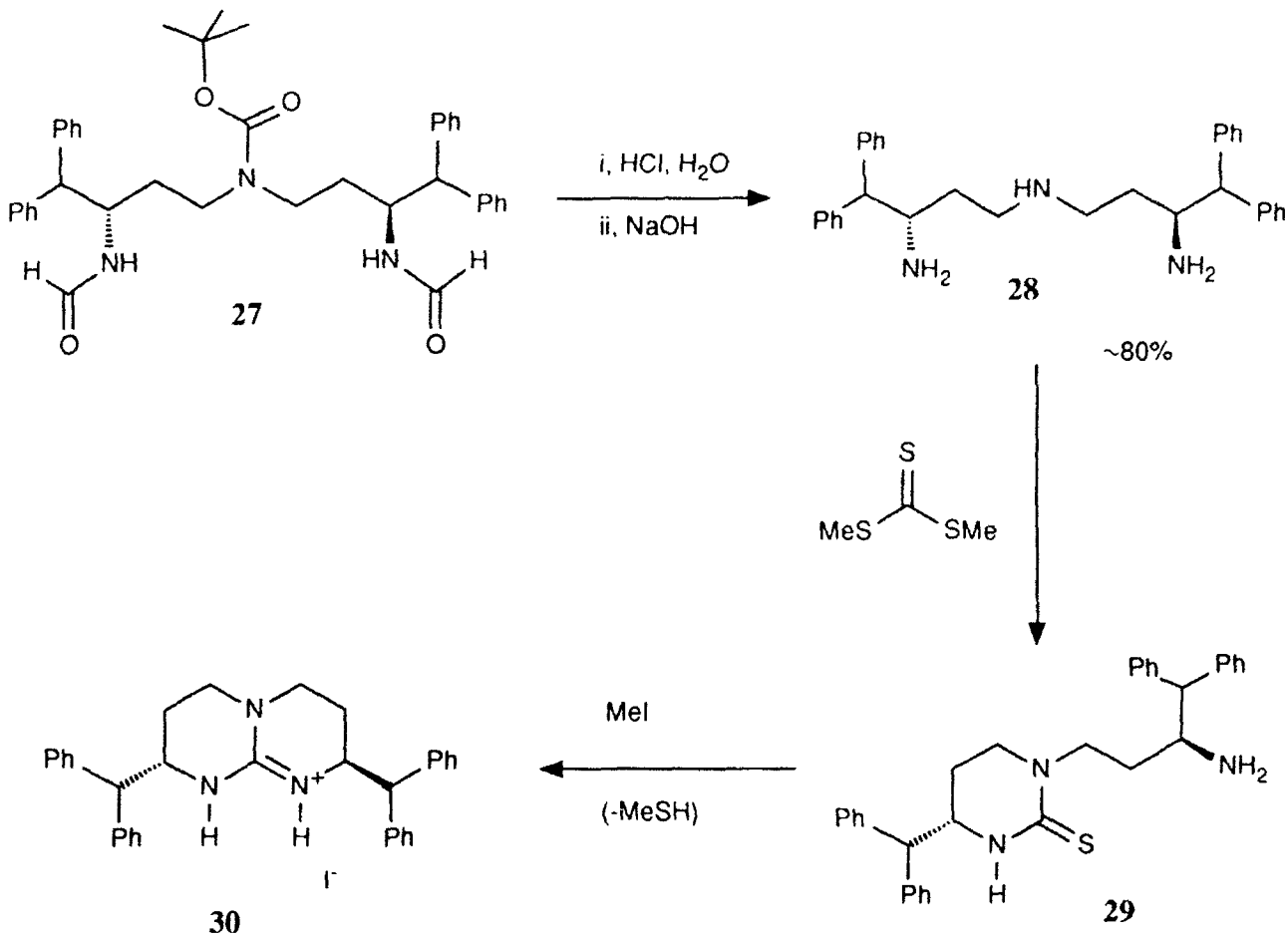


Scheme 3

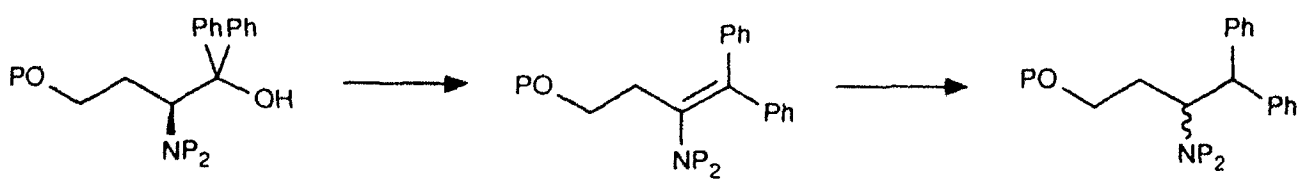
In the event, Scheme 3 was realised as shown in specific detail in Scheme 4. The synthesis was, however, a great deal more problematic than had been anticipated. Part of the difficulty concerned maintenance of the integrity of the asymmetric centre in the early intermediates. Thus, it took some time to develop a workable, large-scale procedure for the preparation of L-homoserine lactone hydrochloride (**25**) from L-methionine, which could be guaranteed to proceed without racemisation. The organometallic addition to give **22** proceeded smoothly, but subsequent hydrogenolysis of the benzylic hydroxyl proved extraordinarily troublesome. Aside from complications



Scheme 4 (contd. over)



Scheme 4 (contd. from previous page)

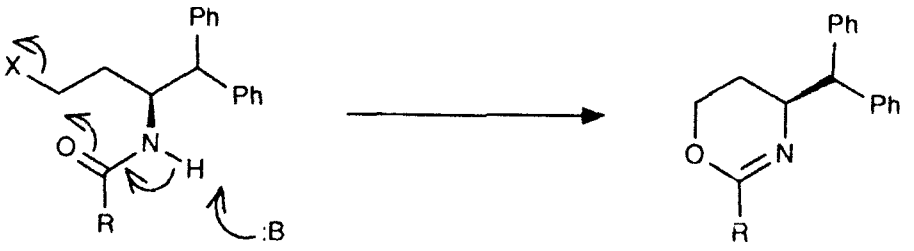


Scheme 5

due to the presence of the other functional groups, it was necessary to guard against an elimination-hydrogenation mechanism (Scheme 5) by which racemisation could take place. After trying many combinations of reagents and protection strategies, we

developed the procedure shown in Scheme 4, giving amino-alcohol **26** in very acceptable yield. Although this was an exceptionally frustrating episode, it is some consolation that we solved a difficult problem which could be of some general interest. The ability to convert the carboxyl group of an amino acid to a bulky diarylmethyl group renders accessible a variety of novel homchiral ligands and auxilaries for asymmetric synthesis.

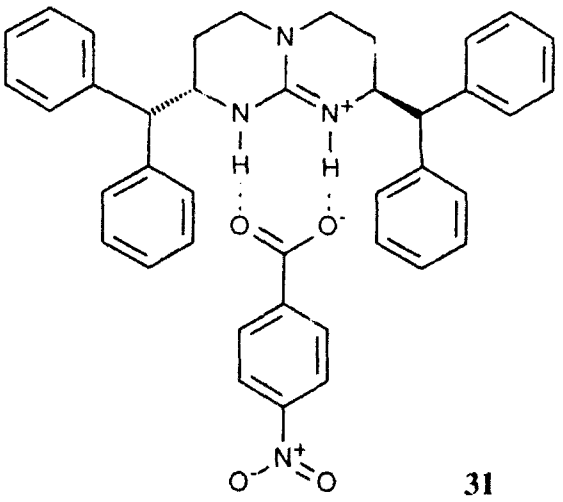
From **26** onwards the asymmetric centre was secure, but a further problem arose in the choice of *N*-protection methodology. The assembly of two of the asymmetric units on a central nitrogen (**23** . **24** in Scheme 3) required that the primary hydroxyl be turned into a leaving group, and that the resulting alkylating agent be reacted with "P'NH_2" (P'= activating and/or protecting substituent). It was inevitable that basic conditions would be required during the second step. The *N*-protecting group P would need to quench the nucleophilicity of the nitrogen, and would also need to be stable to the basic conditions. There was a particular danger of base-induced cyclisation with the common amide and carbamate protecting groups (Scheme 6); this process was indeed observed for *N*-BOC and *N*-acetyl derivatives. As shown in Scheme 4, the successful sequence involved protection of the nitrogen by incorporation in a pyrrole ring. We had previously noted in another context that this may be the only way of suppressing nitrogen nucleophilicity without introducing sensitivity to basic conditions,[5] and we were not displeased to be able to reinforce the point by using the method a second time.



Scheme 6

Once the problem of *N*-protection had been solved the synthesis of protected triamine **27** proceeded fairly smoothly. Conversion of **27** to guanidinium hydroiodide **30** did not require any novel procedures, the stepwise bicyclisation *via* **29** having been developed by other workers.[6] Even so it proved unusually troublesome because of difficulties in handling and purification (notably the extreme sensitivity of triamine **28** to atmospheric CO_2). Hydroiodide **30** failed to crystallise, but could be deprotonated to **18** (Ar = Ph) with aqueous NaOH. On exposure to atmospheric CO_2, solutions of the guanidine yielded crystals of a hydrated hydrogen-carbonate for which good analytical and spectroscopic data were obtained.

(iii) *Recognition and catalytic properties of* **18** *(Ar = Ph).* Having synthesized our target, we turned to the investigation of its properties. We were pleased to find evidence for the expected complex formation with carboxylic acids. Thus if solutions of the hydrochloride in $CDCl_3$ were shaken with aqueous sodium *p*-nitrobenzoate, the carboxylate anions were extracted into the organic layer. Consideration of the chemical shifts of the protons on the anion indicated that they were subject to specific shielding effects from the aromatic rings on the guanidinium ion. The guanidinium N-H protons also moved downfield, leaving little doubt that cation and anion were tightly associated, most probably as in **31**. When the *p*-nitrobenzoate was replaced by naproxenate (**32**), as a mixture of R and S forms, similar behaviour was observed. An additional feature was the splitting of the naproxenate signals into two sets of equal intensity, presumably resulting from the two diastereomeric complexes.



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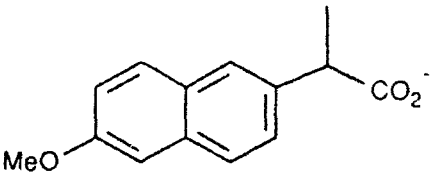

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Unfortunately the behaviour of the guanidine with nitroalkanes was highly disappointing. When used in NMR experiments similar to those described in Section (a)(i) it failed to generate measureable amounts of $CH_3CH{=}NO_2^-$. We were thus unable to investigate the structure of its nitronate complexes by NMR or (as we had hoped), crystallography, and were denied the opportunity to develop a rational explanation of its catalytic properties (on the basis of which a second generation of catalysts might have been designed). The guanidine did prove to be an active catalyst for nitroalkane addition reactions, but only gave very poor enantioselectivities. The key results are summarised in Scheme 7.[7] Our initial trials involved reaction (i), which was attractive because (a) it only involved the formation of one asymmetric centre, and (b) that centre should be formed irreversibly and should be configurationally stable under the reaction conditions

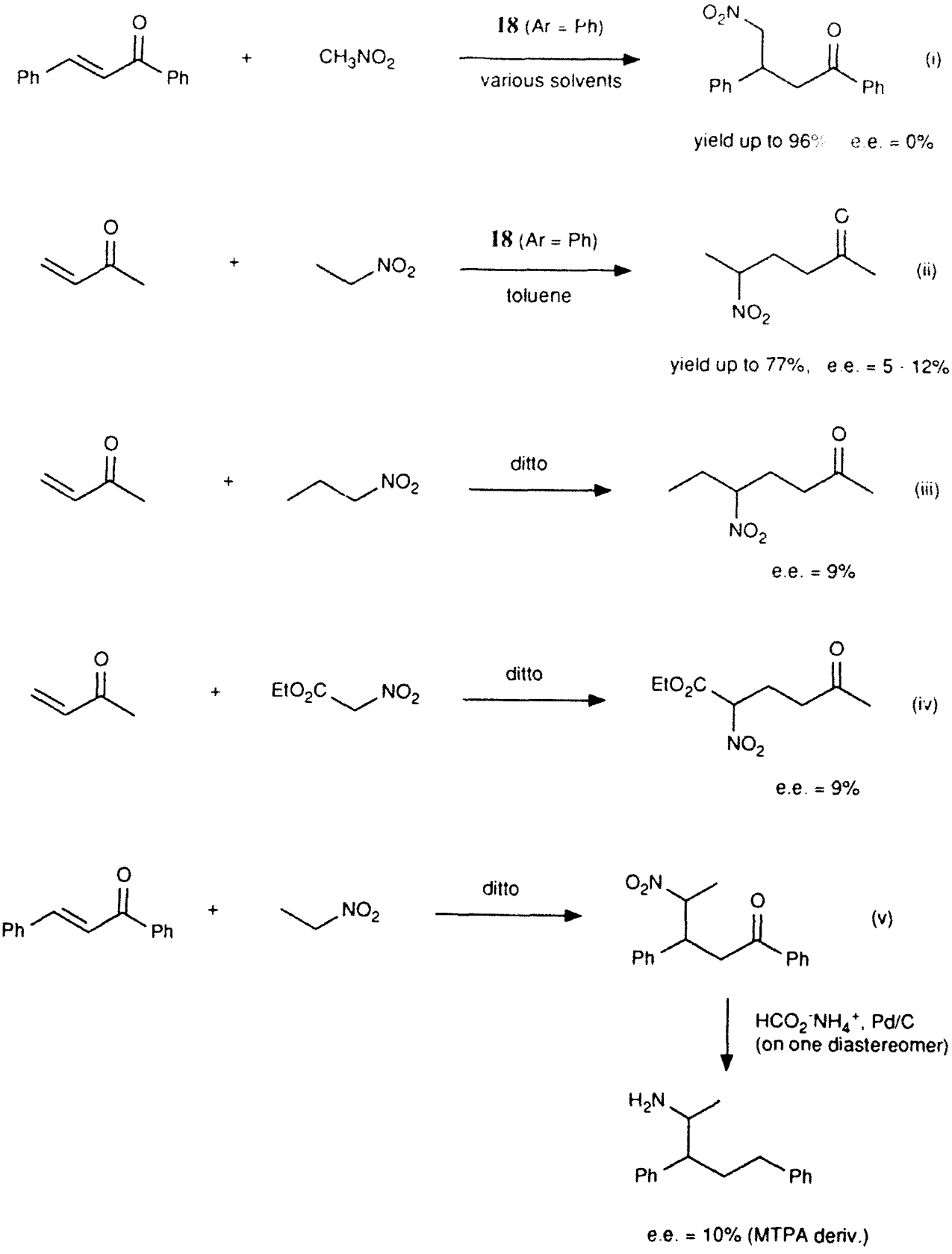
(*vide infra*). As indicated, the reactions proceeded in excellent yields but showed no sign of enantioselectivity whatsoever. Reactions (ii) and (iii) were slightly more successful, but even here the e.e.'s were very modest. In these cases the asymmetric centre was potentially subject to racemisation under basic conditions, and it was indeed found that the best e.e.'s were obtained with the shortest reaction times. Racemisation is not possible for the product of reaction (iv), but once again the e.e. was poor. Finally, reaction (v) gave a mixture of diastereomers, one of which was investigated and again found to have a very modest e.e.

Broadly speaking, this lack of success might be interpreted in two ways. Firstly, the reaction may be occurring *via* doubly H-bonded complexes analogous to **12**, **13** and **14**, but the diphenylmethyl side-chains are not sufficient to induce asymmetry in the product. In this case it might be worth exploring alternative substituents which are more extended and/or contain functional groups capable of imposing greater organisation on the transition states (e.g. by H-bonding). We have in fact made some progress in this direction, developing a method for amino-alcohol **33** in which the aromatic groups are considerably more bulky and contain methoxyls which could potentially be converted to phenolic OH groups in the final product (Scheme 8).

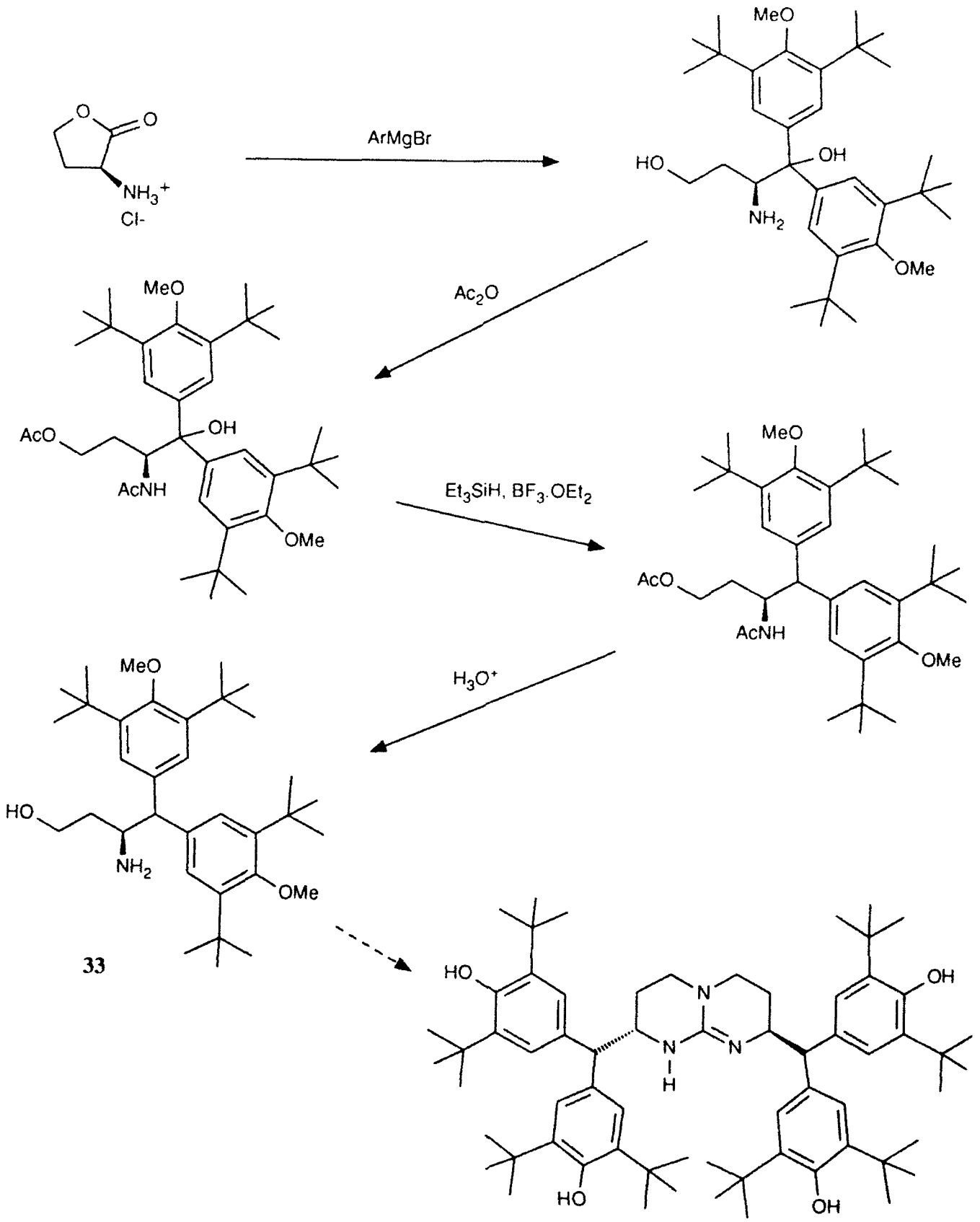
Secondly, it may be that **18** (Ar = Ph) is not able to form the doubly H-bonded complexes, and that reactions are occurring *via* a less well-defined species (perhaps with one N-H....O bond). This interpretation is, of course, supported by the failure of the chiral guanidine to generate $CH_3CH{=}NO_2^-$ species in the NMR experiments described above. The most obvious reason for this failure is that the diphenylmethyl groups are intruding on the space to be occupied by the nitronate. Molecular modelling studies suggest that complex formation should be quite possible, albeit with a greater twist between the anionic and cationic planes than is observed in the crystal structure. However, tne application of the modelling software to the nitronate anions requires certain assumptions which may not be justified, and it may be that an alternative type of association is preferred.

Conclusion

The outcome of this project was not as we had hoped, in that our extensive synthetic effort was not rewarded by significant enantioselectivity in nitroalkane addition reactions. However, we can point to a number of positive results. Firstly, we have characterised the interaction of the bicyclic bases with nitroalkanes to the extent that there can be little doubt that complexes **5** do indeed form as hypothesized. Secondly, in the course of our synthetic work we have solved at least two problems which should have some general relevance. Thirdly, we have synthesized a highly hindered, potent, chiral, C_2-symmetric organic base. While it is ineffective in the rôle for which it was


Ph
Ph
O
+
CH_3NO_2
18 (Ar = Ph)
various solvents
O_2N
Ph
Ph
(i)
yield up to 96%
e.e. = 0%
NO_2
18 (Ar = Ph)
toluene
(ii)
yield up to 77%, e.e. = 5 - 12%
ditto
(iii)
e.e. = 9%
EtO_2C
(iv)
e.e. = 9%
(v)
$HCO_2^-NH_4^+$, Pd/C
(on one diastereomer)
H_2N
e.e. = 10% (MTPA deriv.)

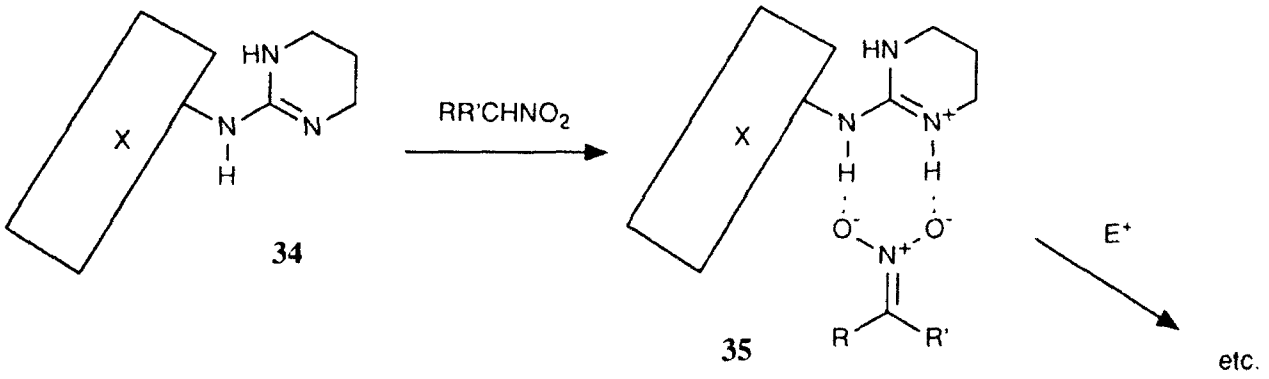
Scheme 7


MeO
ArMgBr
HO
OH
NH2
OMe
NH3+
Cl-
Ac2O
AcO
AcNH
Et3SiH, BF3.OEt2
H3O+
33
N
H

Scheme 8

intended, it seems likely to find some application in synthetic methodology (e.g. in enantioselective dehydrohalogenation reactions[8]).

As for the future of complexes **5** in nitroalkane chemistry, it is of course possible that other bases of general form **18** would succeed where the tetraphenyl compound failed. However, the difficulty of synthesizing such compounds, coupled with the disappointing performance of **18** (Ar = Ph), suggests that an alternative strategy may be preferable. In particular, it is desirable that the design concept should allow structural variation without too much synthetic effort. We are currently planning an approach employing monocyclic guanidines of general form **34** (Scheme 9). The appendage X will need to be carefully designed in order to exert control over the reactive centre in complex **35**. However, by using groups based on a readily-available steroid we believe that a range of potential solutions can be studied with reasonable facility. Further details on these ideas will be given in a proposal soon to be submitted to AFOSR.



Scheme 9

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Deprotonation of Nitroalkanes by Bicyclic Amidine and Guanidine Bases; Evidence for Molecular Recognition within a Catalytic Cycle for C–C Bond Formation

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Deprotonation of Nitroalkanes by Bicyclic Amidine and Guanidine Bases; Evidence for Molecular Recognition within a Catalytic Cycle for C–C Bond Formation

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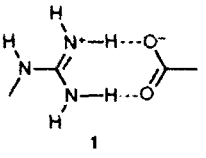
Evidence from ^{1}H NMR spectroscopy, supported by X-ray crystallography, suggests that the bicyclic amidine and guanidine bases **2** and **3** react with nitroalkanes in non-polar organic solvents to give tightly-bound ion pairs **5**; it is argued that homochiral analogues of these complexes may prove valuable as intermediates in enantioselective catalytic C–C bond-forming reactions.

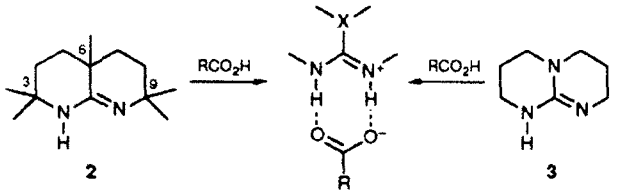
One of the simplest recognition motifs in biological chemistry is the pairing of a carboxylate anion with the guanidinium moiety of arginine, driven by electrostatic attraction and the formation of two parallel H-bonds (*cf.* **1**). For some time it has been appreciated that this interaction can be modelled effectively by using bicyclic amidines and guanidines such as **2**[1] and **3**[2] (Scheme 1) and, in more recent work, homochiral relatives of **3** with C_2 symmetry.[3] It has also been reported that the cations derived from these bases can complex inorganic oxoanions.[1a,2b,3c,3d,4] However, as far as we are aware, there has been no study of the interaction between such cations and carbanionic species. In particular, there is a clear electronic similarity between carboxylates and nitronate anions **4**, suggesting quite strongly that the latter might bind to the bicyclic cations as in **5**. We now report spectroscopic evidence that this does indeed occur in nonpolar and moderately polar organic solvents. We also describe an X-ray crystal structure which demonstrates the interaction in the solid state.

The results assume a special significance when it is considered that nitronates are intermediates in addition reactions of nitroalkanes in which chiral centres may be generated, and which may be induced by catalytic quantities of organic bases (Scheme 2).[5] The potential presence of a tightly organised complex such as **5** within a catalytic cycle raises the possibility that, with an appropriately designed bicyclic base, asymmetric induction might occur from catalyst to product leading to new enantioselective catalytic methodology.

In an initial series of experiments, ^{1}H NMR spectroscopy was used to investigate the interaction of nitroethane in CD_3CN with Eschenmoser's amidine **2** and, as a control, the

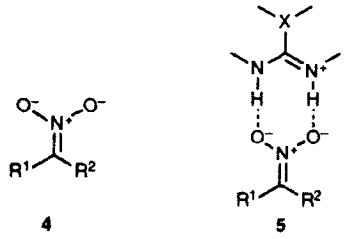


1



2 3

Scheme 1



4 5

'tertiary' amidine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **6**). In the latter case, with the concentrations of both components at *ca.* 1 mol dm^{-3}, the DBU caused the signals due to the nitroalkane α-protons to broaden somewhat (presumably due to exchange), but the spectrum showed no indication that the degree of proton transfer was substantial. This result was expected on the basis of pK_a measurements in acetonitrile by Schwesinger (DBU, 24.3; nitroalkanes, 28.6–30.4).[6]† However, when amidine **2** was added to the solution of nitroethane, the CH_2–NO_2 signal (δ 4.44, q, *J* 7.5 Hz) decreased in size and a new quartet appeared at δ 5.74 (*J* 5.8 Hz). This could be assigned with confidence to the methine proton of nitronate **7**, by comparison with the figures for the corresponding proton in silyl nitronate **8** (δ 6.15, *J* 6 Hz).[10]

The studies were extended to cover the reaction of nitroethane with **2** and **6** in C_6D_6, and with guanidines **3** and **9** in CD_3CN and C_6D_6. The results are summarised in Table 1. It can be seen that there is a major difference in behaviour between bases **2** and **3** on the one hand, and the 'control' molecules **6** and **9** on the other. In all the experiments involving **2** and **3**, the NMR spectra contained sharp multiplets due to nitronate **7** (as well as the methine quartet, the doublet due to $CH_3CHNO_2^-$ could be resolved in many cases). Proton transfer was substantial in both solvents with amidine **2**, and essentially quantitative with guanidine **3**. In the experiments involving **6** and **9**, proton transfer was only observed in one case (entry 7), in which the stronger base and the more polar solvent were employed (moreover, in this example the spectrum of the anion was qualitatively different from the other cases, the methine appearing as a broad singlet). Perhaps the most striking contrast is between entries 6 and 8; nitroethane in C_6D_6 is deprotonated quantitatively by **3**, but left untouched by its 'tertiary' analogue **9**.

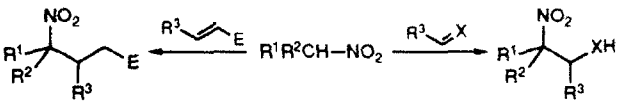
It does not seem reasonable to explain these data simply on the basis of pK_a differences between the four bases. Although it has been shown by Schwesinger that, in acetonitrile, **3** (pK_a 25.96) is a slightly stronger base than **9** (pK_a 25.43),[6] the difference is surely insufficient to account for their contrasting behaviour in these experiments.‡ As far as we are aware, the pK_a of **2** has not been measured in a nonpolar solvent, but there is no reason to suppose that it would be substantially more basic than DBU. The most credible explanation for the results in Table 1 is that the exceptional ability of **2** and **3** to deprotonate the nitroalkane is due to the formation of complexes **10** and **11**, in which the nitronate is stabilised by formation of two, specifically directed H-bonds.

As part of our search for a crystalline analogue of **10** or **11** suitable for structure determination by X-ray diffraction (see below) we undertook some experiments involving phenylnitromethane **12**. This nitroalkane was expected to be more susceptible to deprotonation than nitroethane, and was indeed found to react nearly quantitatively with amidine **2** in C_6D_6 to give complex **13** (Scheme 3). An advantage of this

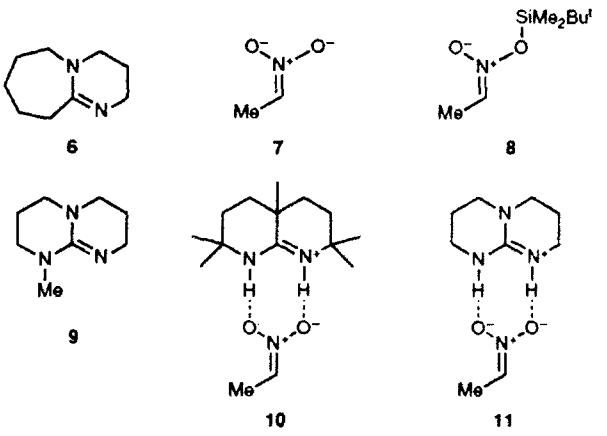
Table 1 Interaction of nitroethane with amidine and guanidine bases in CD_3CN and C_6D_6, as observed by ^1H NMR spectroscopy

Entry	Base	Solvent	Concentrations[a]/ mol dm^{-3}	Result[b]
1	**2**	CD_3CN	0.41, 0.41	[Nitro] : [nitronate], 1 : 1
2	**2**	C_6D_6	0.43, 0.43	[Nitro] : [nitronate], 3 : 1
3	**6**	CD_3CN	1, 1	CH_2–NO_2 signal broadened
4	**6**	C_6D_6	1, 1	No observable interaction
5	**3**	CD_3CN	—[c], 0.23	*Ca.* quantitative proton transfer
6	**3**	C_6D_6	—[c], 0.7	*Ca.* quantitative proton transfer
7	**9**	CD_3CN	0.3, 0.3	[Nitro] : [nitronate], 2.4 : 1
8	**9**	C_6D_6	0.7, 0.7	No observable interaction

[a] Initial concentrations, first figure refers to nitroethane, second to base. [b] Ratios by NMR integration. [c] Incremental addition of nitroethane.



Scheme 2 E = electron-withdrawing group



6 7 8 9 10 11

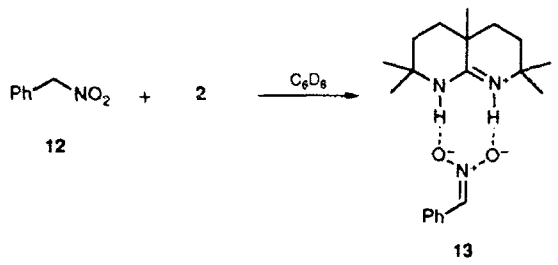
† Although nitroalkanes are remarkably acidic in water, so that proton transfer presumably would occur in that solvent (*cf.* the aqueous pK_a values of $MeNO_2$, 10.2,[7] and acetamidine, 12.52[8]), they are far less so in nonhydroxylic solvents.[9] It is generally understood that the difference is due to the stabilisation of nitronate anions by hydrogen bonding.

‡ The difference of 0.53 pK_a units translates to an equilibrium constant of only 3.4 for proton transfer between the two bases.

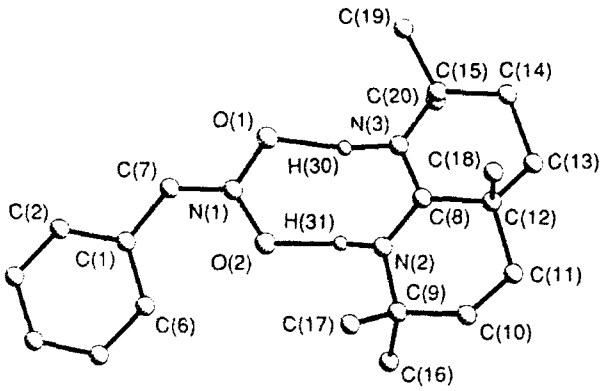
Table 2 Chemical shifts for the amidine–amidinium methyl groups in **2**, and in its reaction products with nitroalkanes in C_6D_6

	δ(3-Me, 9-Me)[b]	δ(6-Me)[b]
Bicyclic amidine **2**	1.12, 1.07	1.15
Phenylnitromethane-derived complex **13**	1.23, 1.16	0.70
Nitroethane-derived complex **10**	1.19, 1.12[a]	0.89[a]

[a] By extrapolation from the spectrum of a solution in which **2** was estimated to be 93% protonated. [b] See formula (Scheme 1) for numbering.



Scheme 3



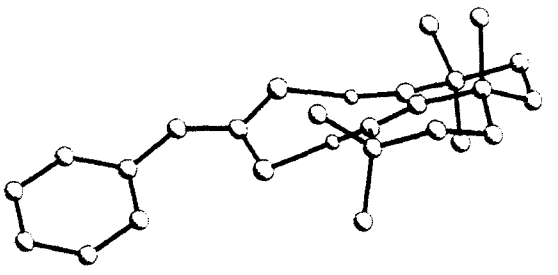
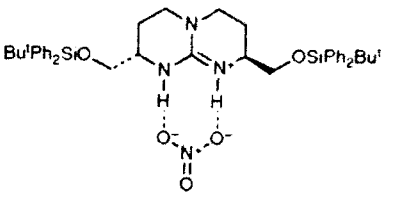
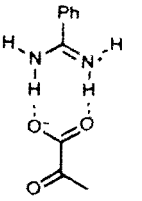


Fig. 1 The X-ray crystal structure of complex **13**, viewed from two different perspectives.

system was that the extent of reaction facilitated the study of the NMR signals due to the amidinium portion of complex **13**. In all the experiments reported herein, only one set of signals was observed for the amidine or guanidine, implying that (unlike the nitroalkane–nitronate interconversion) exchange between protonated and unprotonated forms of the bases was fast on the NMR time-scale (this could occur by direct reaction between free base and corresponding complex, or alternatively by proton exchange between free base and a low concentration of separated cation). On incremental addition





of **12** to **2**, it was possible to follow the movement of the three signals due to the methyl groups in the amidine up to the point where the base was completely protonated (slight excess of **12**). The results are given in Table 2. In general it would be predicted that protonation of **2** should cause all three signals to move downfield.[1a] While this expectation is borne out in the case of the methyl groups on C-3 and C-9 (although the effect is small), the resonance due to the methyl on C-6 moved sharply upfield by *ca.* 0.45 ppm. It was possible to get equivalent figures for the reaction of **2** with nitroethane by employing a very large excess of the latter (Table 2). Again the C-6 methyl resonance moved upfield, but this time by only *ca.* 0.26 ppm.

Either of the above experiments would, by themselves, provide strong support for complex formation, in that it would be hard to explain the movement of the C-6 methyl resonance without invoking a through-space effect from anion to cation. The fact that the size of the effect is dependent on the carbon framework of the anion provides an even clearer indication that our hypothesis is correct.

Finally, one of the first indications of complex formation was the observation that the amidine **2** and nitroethane, which are both liquids, undergo an apparently instantaneous reaction on mixing to give a colourless solid mass. Similar behaviour was noted for **2** and 2-nitropropane. Although neither combination could be persuaded to yield crystals suitable for X-ray diffraction, the pairing of **2** and phenylnitromethane **12** proved more productive. Treatment of **2** with one equivalent of **12** in benzene yielded colourless transparent needles which clouded on evacuation or prolonged exposure to the atmosphere but could be analysed by X-ray crystallography if maintained in an atmosphere of the solvent.

The resulting structure is shown from two perspectives in Fig. 1.§ A molecule of benzene is present in the unit cell and is

§ *Crystal data*: $C_{20}H_{31}O_2N_3 \cdot C_6H_6$, M = 423.598, monoclinic, a = 10.382(2), b = 5.993(1), c = 20.392(4) Å, β = 104.37(2)°, U = 1229.1(4) Å^3 (by least-squares refinement on the setting angles of 22 reflections, λ = 0.71069 Å), space group *Pn* (no. 7), Z = 2, D_c = 1.144 g cm^{-1}, $F(000)$ = 460. Colourless air-sensitive (loss of solvent) platelets, μ(Mo-Kα) = 0.4 cm^{-1}. *Data collection and processing*: Enraf-Nonius CAD4 diffractometer, ω–2θ mode with ω scan width = 0.8 + 0.35 tanθ, maximum collection time 60 s, graphite monochromated Mo-Kα radiation; 2005 reflections measured from two crystals ($1 \leq \theta \leq 22$, $\pm h$, $+k$, $+l$), 1454 unique (merging R = 0.0486 for two data sets after individual decay corrections), giving 1298 with $|F_o| > 5\sigma(|F_o|)$. *Structure analysis and refinement*: Direct methods followed by difference Fourier synthesis. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogens except bridging N*H* in calculated positions, each environment having overall refined U_{iso} [CH U = 0.083(9), CH_2 U = 0.078(7), CH_3 U = 0.104(7), bridging U = 0.08 (1) Å^2], the solvent molecule isotropic with common U_{iso} [C 0.097(1), H 0.27(2) Å]. The weighting scheme $w = 1/[\sigma^2(F_o) + 0.002F_o^2]$ gave flat analysis of variance. The final R values are 0.0565, 0.0617. The programs SHELXS and SHELX-76 are used by kind permission of Prof. G. F. Sheldrick (University of Göttingen). Atomic coordinates, bond lengths and angles, and thermal parameters, have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

omitted for clarity. The relative positions of the two ions clearly indicate the expected hydrogen bonding pattern, as in **13**. The interionic distances O(1)–H(30) (1.64 Å), O(2)–H(31) (1.76 Å), O(1)–N(3) (2.77 Å) and O(2)–N(2) (2.76 Å) may be compared with those in analogous structures such as **14**[3d] and **15**.[11]¶ The internal geometry of the anion is similar to that reported for lithium phenylnitronate by Boche and coworkers.[12]

The C(12)–C(8) and N(1)–C(7) bonds are almost colinear [angles C(12)–C(8)–N(1) 173°, C(8)–N(1)–C(7) 170°] but the two π-systems are not coplanar, being somewhat twisted relative to each other along the C(12)–C(8) and N(1)–C(7) axes [dihedrals O(2)–N(1)–C(8)–N(2) 37°, O(1)–N(1)–C(8)–N(3) 27°]. This is also consistent with our expectations. While hydrogen bonds generally tend to adopt an extended arrangement (which would imply coplanarity in this case), this is not rigidly enforced and a good deal of variation occurs. Relevant examples are to be found in the work of Etter on the crystal structures of nitroanilines.[13]

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¶ Owing to the difficulty in accurately locating hydrogen atoms by X-ray crystallography, the O·····N rather than the O·····H distances provide the more meaningful comparisons.

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